Transplantation of the Heart

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THERE ARE six major problems in the transplantation of the heart or indeed of any vital organ. A brief consideration of these will help us to understand the problems that surgeons and research workers have had to study and overcome.

1. Technical and operative

These involve the actual surgical technique of the transplantation procedure and, in the case of the heart, form a relatively simple problem which has largely been solved by contemporary cardiac surgery.

2. Physiological

Will the transplanted heart—which has no external nerves supplying it—function properly ? Will it be able to support an adequate circulation ? What will be its response to exercise ? These, and many other problems, have largely been answered by research work beginning in the early part of this century. It has been found that the transplanted heart can function adequately despite the absence of its external nerves ; it beats regularly at its own inborn, intrinsic rate which is slower than usual but can speed up under conditions of stress when it is stimulated by adrenaline and other similar hormones circulating in the blood.

3. Immunological

Early research revealed that the *allografted** heart was just as susceptible to "*rejection*" as the transplanted heart. The recipient of the new organ reacts against it in a similar way to its reaction to invading bacteria and, within a few days, the transplanted organ is destroyed. This is termed the "*immune response*" of the recipient's body to the tranasplanted organ. Various types of therapy have been tried to prevent or suppress this response and, although considerable success has been obtained, particularly in relation to kidney grafts, the immune reaction still presents one of the major problems in the transplantation of any organ.

4. Preservation of the Donor Organ

Unless transplantation is to be carried out immediately the donor heart must be preserved by some means from the moment of death of the donor to the completion of the surgical procedure of suturing the heart into the recipient's body. If this time is less than one or possibly two hours, no special preservation procedures are necessary, but if a longer period is expected then the heart must be cooled or perfused with oxygenated fluid (or by a combination of these methods) to maintain the viability of the heart muscle.

This problem of the preservation of the donor heart is a very important one, for if the organ could be preserved for several hours the emergency nature of the transplantation procedure would be overcome and thus make the organisation simpler and the success of the operation more likely. If the heart could be preserved for even longer—several days or even weeks—then the organ could be preserved until tissue typing revealed a well-matched recipient, thus minimising the chance of rejection of the heart, as we shall discuss later.

5. Preservation of the Recipient during the Transplantation Procedure

Obviously the patient who is to be given a new heart must be kept alive during the actual operation. His own diseased heart is to be removed and the donor heart will be sutured into its place. During the operation, the patient's brain and other vital organs are kept alive by the heart-lung machine (pump-oxygenator) which takes over the functions of the heart and lungs by pumping oxygenated blood around the body. Unfortunately, this machine can only be used for a few hours at a time as it causes some damage to the blood cells.

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This article by Dr. Cooper was the subject of a lecture given by him at the Francis Newton Hospital, Ferozepur, in December 1969.

* *Allograft or homograft = organ transplanted from an animal of one species to another, animal of the same species. (e.g. man to man).*

6. Ethical and Organisational

Transplantation of the heart causes strong reactions from many people, some of whom have religious or other objections to the procedure. Many people worry that hearts will be taken from donors before they are really dead. These fears can only be overcome if the doctors involved in these operations build up the confidence of the public by ensuring that each patient receives the fullest possible care and attention, and is only considered as a potential donor (of organs) after his or her death. The organisation involved in transplantation procedures is considerable, large teams of doctors and nurses being required to look after the donor and the recipient. This concentrated care must continue for several weeks or even months after the operation and is, therefore, a heavy burden on the resources of even the largest and best equipped hospitals.

THE EXPERIMENTAL DEVELOPMENT OF HEART TRANSPLANTATION

Research workers began experimenting in this subject as far back as 1905, when two surgeons in the U.S.A. (Carrel and Guthrie) transplanted the heart of one dog into the neck of another. When the transplanted organ is in a site which differs from its usual anatomical position as in this case, the graft is said to be in a *heterotopic* position. This technique allowed them to study the action of the transplanted heart even though it was in a very unusual anatomical position. They were also able to observe the immne response and watch the donor heart being rejected within a few days. Later workers used similar techniques to study drugs which prevented this rejection to a certain extent ; such drugs were said to cause "*immunosuppression.*"

An advance was made in 1946 when a surgeon in the U.S.S.R. (Demikhov) transplanted the second heart into the chest of the recipient animal alongside the recipient's own heart and used it as an auxillary pump.

It was not until the development of the pump-oxygenator—which could, take over the circulation of the entire body—in the 1960's, however, that the recipient animal's own heart could actually be removed and the donor heart sutured into its place ; this procedure is termed *orthotopic* heart transplantation. Much of this work was carried out in the 1960's by two American surgeons (Lower and Shumway) who developed a technique which forms the basis of that used in human heart transplants today. This technique is a fairly simple one and is illustrated in Fig. I.

When surgeons had solved many of the technical problems involved and had studied the physiological problems, they turned to the immunological aspects of this work. Various immunosuppressive agents have been studied experimentally, but cardiac surgeons were fortunate to be able to learn a great deal from the experience already gained by those working in the field of kidney transplantation which had developed a few years previously.

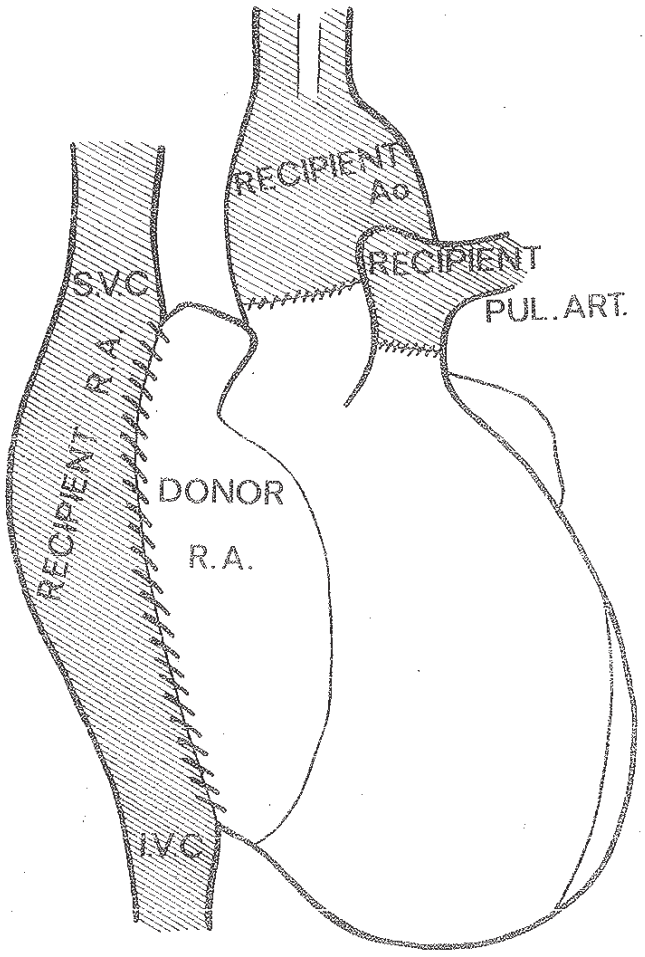

Figure 1 : Diagram to show the surgical technique of orthotopic heart transplantation. (SVC=Superior vena cava; IVC=Inferior Vena cava ; Ao=Aorta ; RA=Right atrium; Pul. Art=Pulmonary artery.

Finally, surgeons felt ready to attempt heart transplantation in patients suffering from incurable heart disease, generally as a result of coronary thrombosis. It is not generally known that the first surgeon to transplant a heart was James Hardy working in the U.S.A. in 1964. He transplanted the heart of a chimpanzee into a patient who was on the point of death from heart failure as the result of severe coronary artery disease. Such a graft from an animal of one species to that of a different species is termed a *xenograft* or *heterograft.* Unfortunately, the chimpanzee's heart was not large enough to fully support the circulation of the patient and it failed an hour after the end of the operation. As is well known, Professor Christiaan Barnard of South Africa performed the first human cardiac homotransplantation in 1967, and since then well over 100 patients have received heart transplants.

THE IMMUNE RESPONSE

Even though surgeons have overcome most of the technical problems involved, and even though the transplanted heart can function very satisfactorily, the body's immune reaction to it has still not been fully overcome. The body recognises all foreign tissue, such as bacteria and transplanted organs, in the same way and unfortunately cannot distinguish one from the other. It has a standard protective reaction to whatever foreign tissue it recognises, and this reaction is aimed at destroying this new tissue. This immune response is, of course, highly valuable and, in fact, life-saving, when the body is invaded by bacteria, but disastrous when the foreign tissue is a transplanted heart.

The immune response can be divided into two main parts :—

(a) **a humoral response**, in which the body produces antibodies which circulate in the blood and which neutralize the antigens of the donor heart rather in the same way the body produces antibodies against various viruses.

(b) **a cellular response** in which some of the white blood cells, the lymphocytes, travel in the blood to the transplanted heart, where they infiltrate the coronary vessels and the myocardium, finally causing heart failure by occlusion of the blood vessels and destruction of the heart muscle.

If unopposed by immunosuppressive drugs, the immune response can destory a transplanted heart within a few days—generally within seven to fourteen days.

TISSUE TYPING

The immune response of the recipient varies from being strong, if the donor tissues are very different from those of the recipient, too weak if the two tissues show certain similarities. If the tissues are identical, as in identical twins, there is no immune response and, therefore, rejection does not occur. This fact allowed successful renal transplantation to be carried out between identical twins, but, of course, cannot be of value in the field of heart transplantation unless one twin happens to die when the other twin is in need of a heart transplant—a very unlikely coincidence.

If there is similarity between the tissues of two people, as may occur in siblings and other relatives there is said to be only a weak incompatibility between these tissues. If donor and recipient are totally unrelated there is a greater chance of incompatibility. There is a wide range of histocompatibility, and the chances of a grafted heart succeeding are thought to be greater where the incompatibility is slight ; less immunosuppression will be required in these cases for the immune response will be less marked.

The tissues of both donor and recipient can be studied and the degree of incompatibility measured by a method known as tissue typing. This procedure has many similarities to red blood cell grouping, but is carrid out commonly on the lymphocytes of the blood. Today, most surgeons would not transplant a heart unless the tissue matching was good, indicating that rejection of the donor heart would be relatively mild.

It should be noted that the immune response is extremely severe and rapid (often occurring within minutes or hours) in xenografted organs, though the actual response is of a slightly different nature than in allografted organs.

IMMUNOSUPPRESSION

Even when tissue typing shows considerable compatibility between donor and recipient cells, some degree of rejection will occur. Many methods have been used, both experimentally and clinically, to try to minimise this immune response, but certain drugs which have an immunosuppressive effect have been found to be most satisfactory to date.

The three main groups of drugs in use at the present are :—

(1) **Azathioprine** (Imuran)—this is one of the group of cytotoxic drugs which have been found to be valuable in treating certain forms of malignancy, notably the leukaemias and reticuloses. These drugs have a toxic effect on all cells in the body but have their greatest effect on those cells which are reproducing rapidly, *e.g.* malignant cells. The lymphocytes which are involved in the rejection of the transplanted heart are also reproducing rapidly and are, therefore, also destroyed by drugs such as Azathioprine.

Unfortunately, as has already been mentioned, white blood cells also protect the body against invading bacteria. Azathioprine, therefore, lowers the body's resistance to infection by depleting the number of lymphocytes present in the blood. As a result of this fact many patients with transplanted hearts have died from infection, while the heart itself has shown little sign of rejection.

(2) **Prednisolone** or similar steroid—certain of the steroid drugs have been found to be valuable adjuncts to Azathioprine, though their mode of action is poorly understood.

(3) **Anti-Lymphocyte serum** (ALS)—this serum is produced in a rather ingenious way. Some of the recipient's lymphocytes are injected into a horse who recognises them as foreign cells and, therefore, sets up an immune response to them. The serum of the horse then contains antibodies which act against these lymphocytes and is, therefore, called anti-lymphocyte serum (A-S). When that patient then receives a transplanted organ. some of this horse serum is injected into his blood and helps to inactivate some of the recipient's lymphocytes before they can act against the donor organ, thus protecting that organ from rejection.

TRANSPLANTATION OF THE HEART AND BOTH LUNGS

As longstanding heart disease can lead to lung damage, and prolonged pulmonary disease can equally lead to cardiac damage, there is likely to be an unknown, though possibly large, number of patients who would benefit from transplantation of the heart together with both lungs. All of the problems affecting transplantation of the heart alone are, of course, involved in this procedure, but, in addition, the problems of lung transplantation are also introduced.

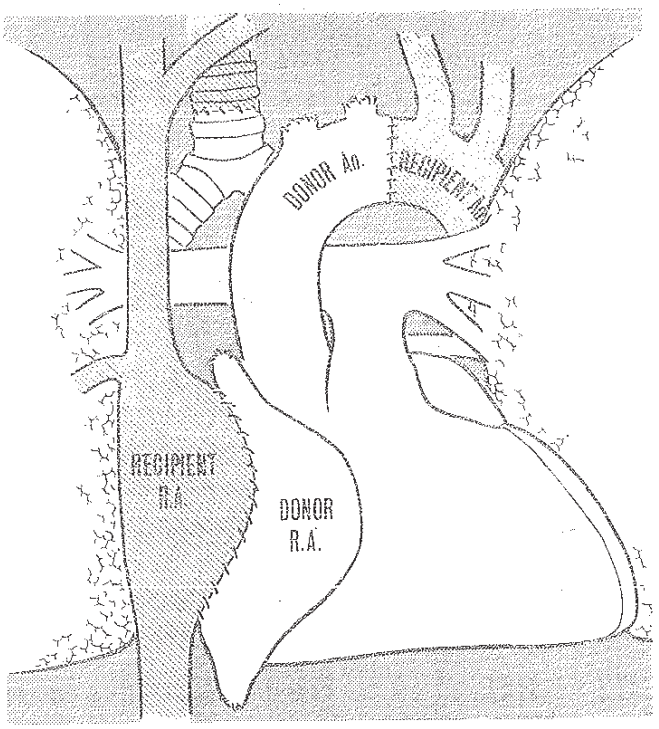

Figure 2: Diagram to show the surgical technique of orthotopic transplantation of the heart and both lungs. (Ao= Aorta; RA=Right atrium)

The actual operative technique is surprisingly no more complex than that of transplantation of the heart alone (Fig. 2). The lungs, however, are rejected probably even more rapidly than the heart, and the occurrence of infection in them is also a major problem. A further problem has also been found in certain experimental animals, though it is not yet certin whether it will be found in the clinical situation in man; this problem involves the loss of respiration following division of the nerves to the lungs which is, of course, an essential procedure when the lungs are being transplanted. Whereas the heart continues to beat adequately after loss of its nerve supply, respiration is inadequate after division of the nerves to both lungs. This problem is not met when only one lung is transplanted.

THE SIZE OF THE PROBLEM

Literally millions of people die each year of heart disease of one kind or another; atherosclerosis affecting the coronary arteries and leading to ischaemic heart disease and myocardial infarction is by far the most common cause of heart disease in the world today. It is common in both western and eastern countries. As yet, there is no really effective treatment for it.

In 1965 nearly 160,000 people died from heart disease in England and Wales. Even if only 1% of these would have benefited from successful heart transplantation, this would require nearly 1,600 such operations to be performed in one year. Several large, well-eqipped, experienced teams of surgeons and nurses would be required to work full-time in this field of medicine. This alone would pose great organisational and financial problems.

However, by far the greatest problem would be the provision of an adequate number of donor hearts. The number of potential donors who died in England and Wales in 1965—*i.e.* those patients dying from head injuries or tumours of the brain and spinal cord—was under 12,000. To obtain a large percentage of these hearts in good enough conditions for transplantation purposes poses considerable organisational problems and, until better methods of resuscitating and preserving donor hearts are developed, and until the reluctance of the public and of some members of the medical profession to allow organs to be taken from dead for transplantation purposes are overcome, then only a very small number of such transplantation procedures will be possible each year.

It may eventually prove possible to transplant animal hearts into man—possibly those of apes or of pigs or sheep which are anatomically suitable—or to develop an effective mechanical heart, either of which would solve the problem of donor supply. But until such time, heart transplantation procedures will be seriously limited by the number of donor hearts made available to the surgeons.

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